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By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WOODSON
Certifying Officer

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(b)(2).

INVENTOR(s)/APPLICANT(s)

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☐ Additional inventors are being named on the ___ separately numbered sheets attached hereto.

TITLE OF THE INVENTION (280 characters max)

IMPROVED METHOD OF DELIVERING THYMOSIN β_4 ($T\beta_4$) AND $T\beta_4$ ANALOGUES AND ISOFORMS TO ACUTE AND CHRONIC WOUND SITES

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification *Number of Pages* [3]
☐ Drawing(s) *Number of Sheets* [ ]
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number ___
☐ Other *(specify)* ___

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

☒ Applicant claims small entity status. See 37 CFR 1.27
☒ A check or money order is enclosed to cover the filing fee
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 02-2135
☐ Payment by credit card. Form PTO-2038 is attached.

Filing Fee Amount: **$80.00**

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ___

Respectfully submitted,

SIGNATURE G. F. Rothwell Date March 31, 2003

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USE ONLY FOR FILING PROVISIONAL APPLICATION FOR PATENT

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[redacted]

IMPROVED METHOD OF DELIVERING THYMOSIN β_4 ($T\beta_4$) and $T\beta_4$ ANALOGUES AND ISOFORMS TO ACUTE AND CHRONIC WOUND SITES

Technical Field of the Invention

The present invention relates generally to the use of combinations of Factor XIIIIa, fibrin-glue, fibrinogen or fibrin or fragments thereof to specifically bind Thymosin Beta 4 ($T\beta_4$) or its analogues, isoforms, or anti-sense peptides or antibodies to concentrate these small peptides at the wound site for wound treatment and repair. This method of delivery of $T\beta_4$ would increase the stability of $T\beta_4$, reduce inflammation, regulate actin, accelerate cell migration and induce angiogenesis to (i) enable more efficient delivery of $T\beta_4$ to the biological sites of interest, (ii) enhance the efficacy of a product comprising at least $T\beta_4$ or one of its related compounds described herein and (iii) reduce costs.

Background

There are many ways to deliver molecules specific to a biological site such as a wound site. In some cases, especially with small molecules, such as $T\beta_4$, the combination of several products may be a more efficient and less costly way of administering a pharmaceutical or a combination of pharmaceuticals. There are numerous historical examples of such combinations and newer ones under development. Additionally, the means and processes by which molecules are bound add significantly to their efficacy and ability to withstand degradation over time while administered inside or on the body for therapeutic purposes.

Summary of the Invention

The invention relates to $T\beta_4$ and $T\beta_4$ analogues and novel methods to specifically concentrate covalently and bind these small peptides to biological molecules such as fibrin glue, fibrin, and fibrin fragments to enhance their wound healing anti-microbial and inflammatory properties.

In most general terms the invention expands the use of $T\beta_4$, $T\beta_4$ analogues and isoforms especially those specifically bonded to the coagulation protein fibrin to enhance the wound healing anti-inflammatory and anti-microbial properties of $T\beta_4$ at the wound site. It is well established in the art that factor XIIIa cross-links the COOH-terminal portions of the γ and α chains resulting in γ-γ dimer and α-polymers, respectively, and that some large proteins such as fibrinectin, α_2-antiplasmin, and, von Willebrand factor can be cross-linked to the COOH-terminal portion of the α chains. Although it was expected that $T\beta_4$ would be cross-linked to the same regions, it was unexpected that this covalent binding by factor XIIIa of $T\beta_4$ would increase the wound healing anti-inflammatory and anti-microbial activity of this molecule.

This invention provides the first evidence that the fibrinogen and fibrin (A) α chain contains the main sites for covalent incorporation of $T\beta_4$. Further this invention clearly establishes that in fibrin(ogen) the major cross-linking sites for $T\beta_4$ are located in the COOH-terminal half of the αC-domains (residues αC392-610) and that $T\beta_4$ can also be cross-linked to the fibrinogen γ-modules.

The present invention is based on the discovery that $T\beta_4$ and other actin sequestering peptides' fragments and analogues that contain the actin binding motif and amino acid sequence LKKTET are chemotactic for endothelial cells and can be bonded with large protein molecules to produce a desired affect or reduce cost of treatment.

The following are claimed:

1. The invention provides a method for a novel method for co-valently concentrating $T\beta_4$ at the site of a wound by binding of $T\beta_4$ and its analogues, fragments, isoforma and other variations, including oxidized versions, to various molecules and compounds such as fibin, fibrin glue, collagen types 1,2,3,4,5, actin, integrin, growth factors, anti-viral compounds, anti-bacterial compounds, and anti-microbial compounds, among others by the use of factor XIIIα.

2. Covalently or otherwise linking the claimed $T\beta_4$ and related molecules and other actin-sequestering peptides using hydrogen bonding, changing the charge of the molecules, using a circular molecule, among other methods, to stents or other medical devices or molecules used for medical treatment.

3. A novel method for concentrating $T\beta_4$ at the site of acute or chronic wounds and stabilizing and enhancing its activities.

4. A novel method using covalently bound $T\beta_4$ or $T\beta_4$ analogues or isoforms which can be delivered by a spray or bonding formulation to the site of acute or chronic wounds.

5. Applying a therapeutically effective amount of the composition or combination to a site on a periodic basis during a course of therapy to create the desired medical effect.

6. In one aspect of the method, the healing polypeptide is $T\beta_4$ or an isoform or oxidized form delivered in a tolerated dosage formula with a covalently linked larger protein to stabilize and prolong biological activity and to created the desired medical effect.

7. The composition may be naturally derived, or produced using recombinant or synthetic methods.

8. The method of claim 5, wherein the agent in an antibody.

9. The method of claim5, wherein the antibody is polyclonal.

10. The method of claim 5, wherein the antibody is monoclonal.

11. A method for coating a stent with covalently based $T\beta_4$ or $T\beta_4$ isoforms or analogues at the site of a vascular disorder to reduce inflammation and infection and to accelerate wound healing.

12. The method of claim 9, wherein one would use an antagonist of the $T\beta_4$ peptide.